Clinical Question

How Reliably Can Autoimmune Hypophysitis Be Diagnosed Without Pituitary Biopsy

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Abstract

Autoimmune hypophysitis is a rare chronic inflammatory condition of the pituitary gland which typically presents with hypopituitarism and a pituitary mass. Cases involving anterior pituitary alone (65%) are 6 times more common in women, typically presenting during pregnancy or postpartum (57%). Anterior and posterior pituitary involvement (25%) is twice as common in women and neurohypophysis alone (10%) occurs equally in both sexes. It has a prevalence of around 5 per million, an annual incidence of 1 in 7 to 9 million and in our experience represents the known or suspected cause of 0.5% of cases of hypopituitarism, <1% of pituitary masses and 2% of non-functioning macro lesions presenting to an endocrine clinic. However, ‘missed’ cases of autoimmune hypophysitis may be the aetiology of some other unexplained cases of hypopituitarism.

Clinically, headache and visual disturbance are common. Anterior hypopituitarism shows a characteristic but atypical pattern of deficiency of ACTH followed by TSH, gonadotrophins and prolactin deficiency or hyperprolactinaemia. 18% of cases have evidence of another autoimmune condition. On MRI imaging, autoimmune hypophysitis is typically symmetrical and homogeneous with thickened but undisplaced stalk in contrast to typical findings with pituitary tumours.

Ultimately the histological diagnosis of autoimmune hypophysitis can only be confirmed by surgery but a presumptive diagnosis can often be made on the basis of a combination of context and clinical features and pituitary biopsy is not always clinically necessary for effective clinical management of the patient.

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What is autoimmune hypophysitis?

Autoimmune hypophysitis is a rare chronic inflammatory condition which typically presents with hypopituitarism and a pituitary mass. The usual histological appearance is ‘lymphocytic hypophysitis’ with lymphocytic infiltration which may involve only anterior pituitary, only neurohypophysis or both. It is described as autoimmune because of its association with other autoimmune conditions, particularly Hashimoto’s thyroiditis, and because anti-pituitary antibodies have been described in a proportion of cases. Granulomatous hypophysitis is a similar inflammatory pituitary mass which occurs even more rarely and which some authors consider part of the same autoimmune spectrum and others consider distinct. Both conditions share some clinical features with other rare forms of hypophysitis including xanthomatous hypophysitis (considered to be a reaction to components of ruptured cysts or other pituitary lesions) and secondary involvement with systemic inflammatory diseases (sarcoid, Wegener’s, Langerhans cell histiocytosis, TB, syphilis). Autoimmune hypophysitis has also been described in patients undergoing treatment with powerful immunoregulatory drugs such as CTLA-4 blockade for metastatic cancer or interferon and ribavirin for hepatitis C.

Autoimmune hypophysitis is certainly rare in clinic practice. Caturegli et al indentified only 379 cases in the world literature up to 2004 (268 histologically proven), although a current PubMed search (May 2009) identifies over 50 subsequent additional case reports of hypophysitis suggesting that the diagnosis is increasingly recognised. We previously found only 5 cases (0.8%) in 619 consecutive pituitary operations over a 15 year period in our neurosurgical unit which serves a population of approximately 3 million –an annual incidence of 1 in 9 million, consistent with many other series. For this article we undertook an analysis of the Leicester Endocrinology clinical information system database which contains detailed, coded clinical data on all endocrine patients seen over the past 20 years in our clinic (which provides the main focus of specialist endocrine care in Leicestershire UK – approximately 1 million population). We identified only 7 cases in whom hypophysitis had been diagnosed (2 diagnosed elsewhere before moving to the area) including 5 cases proven histologically (2 lymphocytic, 1 mixed lymphocytic/ granulomatous, 1 granulomatous, 1 xanthogranulomatous) and 2 cases who had not undergone surgery but with characteristic pattern of hypopituitarism presenting during or after pregnancy (see below). Searching the same database we found a diagnosis of hypopituitarism in 1300 cases, pituitary tumour in 980 cases (440 “macro” lesions - 270 non-functioning; 560 functioning adenomas) and pituitary surgery in 390 cases.

Thus from the literature and from our own experience, autoimmune hypophysitis appears to have a prevalence of around 5 per million, an annual incidence of 1 in 7 to 9 million and represents approximately 0.5% of cases of hypopituitarism, <1% of pituitary masses and 2% of non-functioning macro lesions presenting to an endocrine clinic. The experience of any one clinician or centre is therefore inevitably limited.
The clinical question posed for this article potentially addresses two related issues: 1) can we reliably diagnose autoimmune hypophysitis in the appropriate clinical context without pituitary surgery and biopsy, and conversely, 2) are we missing cases of autoimmune hypophysitis amongst the many patients who present with hypopituitarism in the absence of a pituitary mass which requires surgery?

What are the clinical features of autoimmune hypophysitis?

The clinical features described in the literature have been reviewed by Caturegli. Autoimmune hypophysitis typically presents with a pituitary mass and hypopituitarism. Inflammation involving only the anterior pituitary (65%) is 6 times more common in women, of whom 57% present during pregnancy or postpartum. Cases which involve anterior and posterior pituitary (25%) are twice as common in women and inflammation involving only the neurohypophysis (10%) occurs equally in both sexes. The condition also occurs rarely in childhood. Headache (46%) and visual disturbance (33%) are common presenting features. Anterior hypopituitarism most commonly involves an atypical but characteristic pattern of deficiency of ACTH followed by TSH, gonadotrophins and prolactin (with failure of lactation, although hyperprolactinaemia is also common). Diabetes insipidus occurs in cases involving the posterior pituitary and is often a reason for suspecting the diagnosis. 18% of cases have evidence of another autoimmune condition – most commonly Hashimoto’s thyroiditis (7%). Pituitary surgery had been performed in 64% of cases, and other treatments used included steroids, immunosuppressant drugs and pituitary radiotherapy. 8% of reported cases had died (in many cases due to presumed undiagnosed and untreated hypoadrenalism) but with appropriate treatment the prognosis appears excellent in most cases. Follow up in the literature is mostly short, but all our cases in Leicester remain in remission 3 to 19 (median 8.6) years after initial diagnosis with some recovery of pituitary deficiencies in 50%.

How do clinical features differ from other pituitary masses?

All the features seen in autoimmune hypophysitis may be seen in any other cause of a pituitary mass, but the balance of symptoms differs from the more common pituitary adenoma. Whilst visual disturbance is common with any large pituitary mass, headache is uncommon with most benign pituitary tumours – except acromegaly and cases of pituitary apoplexy. In our database, headache was a major presenting feature in 43% of cases of hypophysitis, 25% cases of apoplexy, 22% of acromegaly and 11% of non-functioning macroadenomas. It is also of interest that headache is a prominent feature of Tolosa Hunt syndrome, an auto-immune infiltration of the cavernous sinus which usually does not involve the pituitary although cases with hypopituitarism and pituitary mass have been described.

The incidence (and presumably sequence) of anterior pituitary deficiencies described in autoimmune hypophysitis (ACTH > TSH > LH/FSH) differs from the more typical incidence and sequence seen with pituitary tumours, surgery and radiotherapy (GH > LH/FSH > TSH = ACTH). Diabetes insipidus is very
uncommon in uncomplicated and unoperated pituitary adenomas although it does occur with craniopharyngiomas.

On MRI, autoimmune hypophysitis is typically symmetrical and homogeneous with thickened but undisplaced stalk. Pituitary adenomas in contrast are typically asymmetrical, often non-homogeneous, displace the stalk and erode the fossa floor. Craniopharyngiomas and other parasellar tumours have their own well-recognised imaging characteristics. Unfortunately none of these features can differentiate all cases with certainty.

Can diagnosis be predicted before or without surgery?

Ultimately the histological diagnosis of autoimmune hypophysitis can only be confirmed by surgery. Conversely, in both symptomatic and incidentally-discovered cases of pituitary masses felt to be pituitary adenomas, endocrinologists and pituitary surgeons typically and rightly wish to avoid pituitary surgery and its associated risks unless the mass is causing visual problems or problems via invasion of the cavernous sinus, or unless there is doubt about the underlying diagnosis.

Factors which will increase the suspicion of autoimmune hypophysitis include the context (e.g. current or recent pregnancy and presence of other autoimmune disease(s)), an atypical pattern of hormone deficiency (e.g. diabetes insipidus or ACTH deficiency occurring with normal LH/FSH and GH reserve) and a pattern or severity of symptoms out of proportion to the size of the pituitary mass on imaging (particularly the presence of headache in the absence of acromegaly, apoplexy or malignancy).

Imaging features are hard to differentiate with absolute certainty, but all experienced endocrinologists will be familiar on reviewing images with the overall judgement of “that doesn't look like a pituitary adenoma!”.

Thus the presumptive diagnosis of autoimmune hypophysitis can often be made on the basis of a combination of these clinical features

The presence of anti-pituitary antibodies has been described in some cases of autoimmune hypophysitis, but this test is neither sensitive nor specific enough to be used for diagnosis. The autoantigens involved also remain poorly defined and the test is not routinely available in clinical practice.

Are we missing cases by failing to operate, and does it matter?

Several lines of evidence have led to the suggestion that some cases of isolated hypopituitarism (without significant pituitary mass at the time of investigation) might actually represent ‘missed cases’ which are part of the spectrum of autoimmune hypophysitis, including some cases previously diagnosed as Sheehan's syndrome or empty sella syndrome:

- the benign long-term prognosis of most cases of histologically-proven autoimmune hypophysitis.
• the tendency for pituitary masses to resolve on subsequent imaging.

• the presence of anti-pituitary antibodies in over 10% of patients with autoimmune thyroid disease and 1% of controls.\(^{14}\)

• the high incidence of pituitary antibodies in patients with idiopathic hypopituitarism and hyperprolactinaemia.\(^{15-17}\)

• the reported 35% incidence of mild or severe isolated growth hormone deficiency in patients with autoimmune thyroid disease who have pituitary antibodies.\(^{14}\)

We have addressed this issue by searching for atypical presentations of hypopituitarism and associated clinical findings in our database covering 20 years of endocrine practice. We identified 1300 patients with proven or suspected hypopituitarism in one or more axis. We excluded all patients with a diagnosis of autoimmune hypophysitis or with evidence in the database of any pituitary or para-pituitary tumour, pituitary surgery or radiotherapy, congenital brain and pituitary problems, brain injury, onset in infancy and iatrogenic deficiencies. Of the remaining 640 patients with hypopituitarism, 80 had isolated diabetes insipidus and in the other 560 abnormalities of the 6 pituitary axes (vasopressin, ACTH, TSH, gonadotrophin, GH, PRL) were recorded in 1 axis in 65%, 2 axes in 26%, 3 in 7% and 4 or more in 2%.

We then reviewed the original electronic record (including hormone and imaging results and copies of clinic letters) in all patients with DI combined with any anterior pituitary deficiency, all those with 3 or more deficient axes and all 10 with a previous diagnosis of Sheehan’s syndrome, to seek evidence of a history suggestive of autoimmune hypophysitis. Of the 67 cases reviewed, we considered clinically in retrospect that a diagnosis of autoimmune hypophysitis was likely in 4 (6%) and feasible in 66% so that autoimmune hypophysitis has probably been underdiagnosed in our practice, and possibly substantially so.

However, although only surgery can reveal with certainty the nature of any non-functioning pituitary mass, the cautious physician will still ask “If vision is not threatened why accept the risks of operation?”. Where the mass is not causing significant pressure effects other than hypopituitarism it seems hard to justify surgical intervention, and even eminent pituitary surgeons suggest that supportive therapy without surgery is often appropriate.\(^{11}\) Steroid therapy has been advocated to treat the autoimmune mechanism even in cases which have not been histologically proven, but its efficacy is uncertain\(^{1,12}\) and it is therefore hard to justify routinely. When visual pathways are affected, a case can certainly be made for a short trial of steroid treatment where the combination of context (e.g. recent pregnancy), pattern of hormone deficiency and imaging findings are all suggestive of autoimmune hypophysitis.

A clinical approach?
In summary, while conservative management without surgery is frequently appropriate for non-functioning pituitary adenomas which are discovered either incidentally or as the result of the development of hypopituitarism, the endocrinologist always needs to be alert to the possibility of rarer diagnoses for which other treatments may be appropriate and which may only be diagnosed with certainty at pituitary surgery. The rarer alternative diagnoses include autoimmune hypophysitis – but atypical features including headache, unusual patterns of hormone deficiency or atypical imaging appearances may be seen in other conditions including inflammatory masses caused by other multisystem diseases and rarer sellar and parasellar tumours (craniopharyngioma, germinoma, meningioma, chordoma, pituitary metastasis etc). The clinician should consider all these possibilities when atypical features are present – and in some cases other systemic investigations may aid the diagnosis (e.g. inflammatory and retroviral markers, ANCA, ACE, hCG).

Where autoimmune hypophysitis is suspected, and other serious diagnoses effectively excluded, but the patient is clinically well on simple replacement therapy then biopsy may be hard to justify unless alternative treatments with significant adverse effects (prolonged high dose steroids, immunosuppressive agents or pituitary radiotherapy) are being considered.

The answer to the clinical question is thus twofold – “No – Autoimmune Hypophysitis cannot be diagnosed with certainty without pituitary biopsy” – but also – “No – Pituitary biopsy is not always clinically necessary for effective clinical management of the patient”.

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